REMARKS

The Office Action sent November 24, 2009, has been received and reviewed. All claims stand rejected. This application is to be amended as previously set forth. All amendments are made without prejudice or disclaimer. Basis for the amendments can be found throughout the published PCT application (WO2004/025243), for example, at pages 4-5; page 9, lines 19-21; and page 12, lines 7-10. Basis for new claims 15 and 16 can also be found throughout the published PCT application (WO2004/025243), for example, at pages 4-5; page 9, lines 19-21; page 12, lines 7-10; pages 6-7; and the several Examples. No new matter has been presented. Reconsideration is respectfully requested.

35 U.S.C. § 103(a)

Claims 1-7 stand rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Creighton (1993) "Proteins: Structures and Molecular Properties," Second Edition, W.H. Freeman and Company, NY (hereinafter "Creighton") in view of U.S. Patent 6,670,194 (hereinafter "the '194 Patent"). Applicants respectfully traverse the rejection.

To establish a *prima facie* case of obviousness, the prior art itself or "the inferences and creative steps that a person of ordinary skill in the art would [have] employ[ed]" at the time of the invention are to have taught or suggested the claim elements. Additionally, there is to have been "a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements" in the manner claimed. KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1742 (2007). "Often, it will be necessary for a [fact finder] to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed." Id. Furthermore, to establish a *prima facie* case of obviousness, there must have been a reasonable expectation of success. MPEP § 2143.02. Underlying the obvious determination is the fact that statutorily prohibited hindsight cannot be used. KSR Int'l Co., 127 S.Ct. at 1742.

Modifications of prior art references may only support a *prima facie* obviousness determination if there is a reasonable expectation of success in making the proposed

modification. MPEP § 2143.02(I). There is no reasonable expectation of success in making a proposed modification to a reference when the resulting modification would be inoperable. Nor can a proposed modification to a reference change its principle of operation to support a rejection under 35 U.S.C. § 103. MPEP § 2143.01(VI); In re Ratti, 270 F.2d 810 (CCPA 1959).

Moreover, a claim is not obvious in view of a reference that teaches away from the claim. MPEP §§ 2144.02(VI) and 2145(X)(D)(2). A reference is said to "teach away" when a person of ordinary skill, upon reading it, would be discouraged from following the path set out in the reference, "or would be led in a direction divergent from the path taken by the inventor." In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994); Monarch Knitting Mach. Corp. v. Sulzer Morat Gmbh, 139 F.3d 877 (Fed. Cir. 1998); Para-Ordnance Mfg. v. SGS Importers Int'l Inc., 73 F.3d 1085 (Fed. Cir. 1995). A reference must be considered not only for what it expressly teaches, but also for what it fairly inherently suggests. In re Baird, 16 F.3d 380 (Fed. Cir. 1994); In re Graselli, 713 F.2d 731, 743 (Fed. Cir. 1983).

Claims 1-7, and new claim 15

In the Final Office Action of November 24, 2009, the Office asserts that "it would have been obvious to one of ordinary skill in the art to perform the digital chromatography techniques of Creighton on complex samples such as blood, cells, tissues, and fractions thereof (as taught by Aebersold et al.)." Id., at page 7.

In the Amendment of July 13, 2009, applicants amended independent claim 1 to recite, "wherein said compound does not interact with the majority of said molecules." Id., at page 2. It was submitted that this element presented a clear distinction between the claimed subject matter and prior art methods, including the methods of Creighton and the '194 Patent. For example, Creighton and the '194 Patent concern diagonal separation of all cysteine-modified peptides of a single protein, and quantitative analysis of all proteins in a complex mixture, respectively. In response to this observation, the Office asserted,

> When employing the diagonal techniques of Creighton et al. to analyze complex mixtures such as blood, it would seem that the compounds of Creighton et al. would necessarily interact only with a minority of the molecules present in such complex samples. In particular, in view of the general knowledge in the art that blood contains not only proteins but also lipids, cells, vitamins, small molecules, ions, etc., there is a strong

scientific basis to suggest that the compounds, being selective for specific amino acids, would necessarily interact with only a minority of the total molecules present in blood samples...

For these reasons, when employing the diagonal chromatography methods of Creighton to analyze complex samples such as blood, the recited feature would necessarily follow.

(Final Office Action of November 24, 2009, at pages 7-8.)

Thus, the Office seems to equate the methods of Creighton and the '194 Patent, wherein compounds react universally with all proteins and/or peptides in a mixture through certain amino acid side chains, with the subject matter of the present claims. Without agreeing to this reasoning, applicants have amended the claims to recite, "wherein said compound does not interact with the majority of said proteins and/or peptides."

For at least the reason that amended claim 1 specifies that the compound does not react with the majority of proteins and/or peptides in the mixture, claim 1 is clearly distinct from Creighton and the '194 Patent. Neither Creighton nor the '194 Patent mentions anything about a compound that is capable of reacting with less than a majority of the proteins and/or peptides in a sample. In fact, the methods disclosed in each of the cited references necessarily react non-specifically with all proteins and/or peptides in a mixture through their amino acid side chains. In Creighton, only one protein is analyzed, and it interacts completely with the compound used. In the '194 Patent, it is specified that the affinity labeled reagent is designed to react with peptides of each protein in a mixture in order to allow protein quantitative analysis of the whole sample (See Id., *e.g.*, at col. 3, lines 9-15; col. 5, lines 55-60; and col. 15, lines 54-57). To achieve this, the reagent reacts with peptides derived from each and every protein in the sample. Proteins that do not react with a particular reagent may still be targeted by including reactivity to other groups, as described at col. 16, lines 45-52 of the '194 Patent. ("The method can be extended to include reactivity toward other functional groups. A small percentage of proteins (8% for *S. cerevisiae*) contain no cysteinyl residues and are therefore missed by analysis using reagents with sulfhydryl group specificity (*i.e.*, thiol group specificity). Affinity tagged reagents with specificities toward functional groups other than sulfhydryl groups will also make cysteine-free proteins susceptible to analysis.").

Thus, the compounds of the '194 Patent react with at least 92% of the proteins present in the mixture; *i.e.*, with the majority of the proteins and/or peptides, contrary to the present claims. Moreover, the '194 Patent teaches it is desirable to even further increase this coverage, because otherwise the proteins are "missed by analysis." Id. This is not only different from what is taught in the present application, but a clear teaching away from the subject matter of the present claims, as it unambiguously leads one of skill in the art towards compounds that react with more than a minority of proteins in a complex mixture.

Claims 2-7 and 15 are patentable, notwithstanding Creighton and the '194 Patent, at least for the same reasons set forth for claim 1, *supra*. Claims 2-7 depend from claim 1, and therefore contain all the elements of claim 1. Claim 15 recites, *inter alia*, "the compound does not interact with the majority of the plurality of peptides."

New claim 16

New claim 16 is patentable, notwithstanding Creighton and the '194 Patent, at least for reasons similar to those set forth, *supra*, with respect to claim 1. Claim 16 recites, *inter alia*, "adding (a) compound to a complex mixture of molecules, wherein the compound stably and specifically interacts with at least one of the molecules." None of the interactions in Creighton and the '194 Patent is specific. Protein quantification of a sample, as taught by, for example, the '194 Patent, is not the same as isolating specific molecules that selectively interact with a compound of interest. The use of the term, "selectively reactive," in the '194 Patent differs from specificity, as it is defined in the present application, for example, at pages 6-7. For example, while the PRG of the '194 Patent may selectively interact with all proteins and peptides in a sample comprising a particular selected amino acid residue, this does not result in interaction specificity. This step in the '194 Patent serves only to reduce the complexity of a complex mixture for analysis, while still interacting with one peptide of each of all the proteins present in the original mixture. See, the '194 Patent, *e.g.*, at col. 5, lines 55-60; and col. 15, lines 61-66.

Modifying the '194 Patent such that its compound reaction step was specific (*e.g.*, useful in identifying a specific interaction partner) would result in an inoperable method. It would be impossible to conduct quantitative proteomics upon complex mixtures, which is the aim of the '194 Patent, if the reaction step was specific. By definition, a specific interaction is at least one

that does not occur uniformly throughout a sample. Quantitative proteomics, as taught by the '194 Patent, depends upon uniform amplification of peptide fragments of larger proteins across the entire proteome. Thus, the reagents used in the '194 Patent are similar to those used in Creighton; reagents that react at discrete amino acid residues that are components of every protein. If a compound were used in the method of the '194 Patent that was specific (*i.e.*, the compound did not react uniformly across the entire proteome), there would be a loss of information proportional to the specificity of the interaction. This result would obviously defeat the aim of the analysis disclosed in the '194 Patent; "qualitative and quantitative analysis of *global protein expression profiles* in cells and tissues." Id., at Abstract (emphasis added).

Claims 13 and 14

Claim 13 stands rejected as assertedly being unpatentable over Creighton, in view of the '194 Patent, and further in view of U.S. Patents 5,705,351 and 5,474,780. Additionally, claim 14 stands rejected as assertedly being unpatentable over Creighton, in view of the '194 Patent, and further in view of GE Healthcare "Fraction Collectors: Frac-950 and Frac-920," Data file 18-1153-57 AD (May 2001). Applicants respectfully traverse these rejections.

Claims 13 and 14 depend from independent claim 1, and therefore contain all the elements of claim 1. Thus, claims 13 and 14 are patentable for at least the reasons set forth, *supra*, with respect to claim 1 (*e.g.*, none of the references discloses the concept of a compound interacting with a specific interaction partner, while not interacting with the majority of proteins or peptides in a mixture).

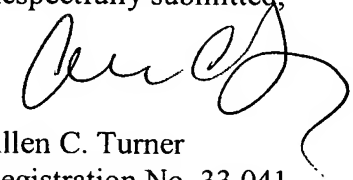
Furthermore, with regard to claim 14, it is noted that the cited GE Healthcare reference only relates to adjusting the size of a particular chromatographic fraction, taking smaller fractions when resolution needs to be improved (to avoid re-mixing of proteins separated on a column). The document relates to single fractions and does not concern pooling of multiple fractions, and more specifically does not concern pooling of non-neighboring fractions (*e.g.*, those with a distinct elution time that are not completely resolved). This is clearly distinct from the subject matter of claim 14, wherein you do not pool adjacent fractions where there is the possibility of overlap (e.g. 1-2-3-4-5), but fractions that elute distinct from each other (e.g. 1-6-11-16-21). See the as-filed Application, *e.g.*, at Example 1.6 and Table 1. This is an additional reason why

claim 14 is patentable in view of Creighton, the '194 Patent, and the GE Healthcare reference.

For at least the foregoing reasons, applicants respectfully request that the rejections of claims under 35 U.S.C. § 103(a) be withdrawn.

In view of the foregoing remarks, the application should be in condition for allowance. If questions remain after consideration of the foregoing, the Office is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,



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